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Is the heart of premature babies born as a result of IVF pregnancy different?

Hearts of premature babies born via IVF

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Abstract
Aim: This prospective study aims to reveal whether preterm births with ART-induced pregnancies are at greater risk of structural and functional cardiac pathologies compared to the control group of preterm births from spontaneous pregnancy.
Material and Methods: Between October 2017 and January 2020, 25 premature babies born by means of assisted reproductive techniques (AC) and 25 babies born from spontaneous pregnancy (SC) were included in the study. All babies recruited for the study were born at or below 34 weeks of gestational age. The groups were evaluated in terms of anatomical, m-mode and tissue Doppler systolic and diastolic functions using transthoracic echocardiography (ECHO).
Results: The groups were found to be similar in terms of anatomical, m-mode and tissue doppler systolic and diastolic functions by transthoracic ECHO (p=0.156).
Discussion: Early diagnosis of possible cardiac diseases is vital for pre- and post-natal management and ultimately for the survival of the infant. Studies should be focused on understanding and eliminating the pathophysiologies increasing the risk of CHD during ever-increasing ART practices.

Keywords
Assisted Reproductive Technology, Heart Defect, Prematurity

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Introduction

Although the frequency and causes of infertility vary across societies, it is estimated to occur in approximately 15% of couples of reproductive age [1]. The highest prevalence of infertility worldwide is in Eastern Europe, North Africa/Middle East, Oceania, and Sub-Saharan Africa [2]. Over the last two decades, the increase in the population seeking help for infertility and the recent developments in Assisted Reproductive Technology (ART), which increases the probability of successful treatment, have led to developments in the field of infertility [3]. This technology includes in vitro fertilization (IVF), embryo culture, fresh and frozen embryo transfer, intracytoplasmic sperm injection (ICSI), preimplantation genetic diagnosis, and IVF with donor oocytes. Although most babies born with ART are healthy, they are thought to have more risk for various aspects of their health than natural pregnancy babies. This idea is based on an increased risk of multiple pregnancies in ART and the consequently increased rate of premature and low birth weight associated with an increased risk of perinatal morbidity and mortality [4]. Besides, the biological and genetic characteristics of the parents with low fertility may add additional health risks for the baby born, and interventions and drugs used for infertility treatment may also cause various complications in the fetus and newborn. Factors such as changing the follicle environment and oocyte structure by artificial stimulation of ovulation, encountering conditions that disrupt the natural functions of the sperm and embryo, freezing and manipulating the oocyte and embryo also may adversely affect this process [5]. Many studies from diverse ethnic populations have shown that embryos conceived after ART have poorer birth outcomes than spontaneously conceived embryos [6,7,8]. Studies have shown that birth defects are more common in these babies [9,10]. Congenital heart defects occur in approximately 0.76% of live births and it is 0.61% after excluding those with underlying genetic diseases [11]. CHDs account for 28% of all birth defects and they lead to a significant rate of morbidity and mortality. On this basis, early diagnosis permits optimal care during pregnancy, delivery, and in the newborn period (including surgical correction of the defect) as well as pregnancy termination for lethal and very severe heart defects. There is not any prospective study on the subject in our country yet. Thus, this study aims to reveal whether preterm birth with ART-induced pregnancies is at greater risk of structural and functional cardiac pathologies compared to the control group of preterm birth from spontaneous pregnancy.

Material and Methods

Study design

It was a prospective study performed at Necmettin Erbakan University in Turkey, between October, 2017 and January 2020. Twenty-five premature babies born by means of assisted reproductive techniques (AC) and 25 babies born from spontaneous pregnancy (SC) were included. All babies recruited for the study were born at or below 34 weeks of gestational age.

Patients with congenital multiple anomalies (chromosomal anomalies, hydrops, spina bifida, patients with major surgical problems, etc.), perinatal asphyxia or metabolic disorders were excluded from the study. Demographic and clinical information of the infants and mothers were recorded. Gestational week of the baby, birth weight, gender, mode of delivery, multiple pregnancy status, 1st and 5th-minute Apgar scores, whether resuscitation was applied or not, surfactant was given or not, existence or non-existence of respiratory distress syndrome, patent ductus arteriosus, bronchopulmonary dysplasia, retinopathy of prematurity, pregnancy mom's weight gain by week during pregnancy, invasive and non-invasive mechanical ventilator time, free oxygen intake time, discharge time and exitus status, age of the mother, comorbidities, if any, non-vitamin drugs used, prenatal steroid use were recorded. The groups were evaluated in terms of anatomical, m-mode and tissue Doppler systolic and diastolic functions using transthoracic echocardiography (ECHO).

Echocardiographic evaluation technique

Babies in both groups were evaluated underwent echocardiographic examination before they were discharged from the neonatal unit, while their clinical status was stable. Before echocardiography, all newborn infants underwent detailed cardiac examination. All echocardiographic assessments were performed by an experienced pediatric cardiologist with 15 years of experience using the GE, Vivid T8, China device. All data were recorded.

Ethics

Ethics Committee approval for this study was obtained from Necmettin Erbakan University with the Ethics Committee decision number of 2017/1026.

Statistical analysis

Data entry, statistical analysis and reporting procedures were performed electronically. Descriptive analysis was performed for the demographic and clinical characteristics of the patients. The distribution of data was assessed using a one-sample Shapiro-Wilk test. Data are demonstrated as mean ± standard deviation for normally distributed continuous variables and frequencies (percentile) for categorical variables. When the values between different groups are suitable for normal distribution, they were compared using the T-test, when not normally distributed, they were compared using the Mann-Whitney U test.

The x2 test was used to assess differences between categorical variables. Test results with $p<0.05$ were considered statistically significant.

Results

Table 1 summarizes demographic characteristics of the patient. Infants in the AC and SC groups were similar in terms of demographic characteristics.

Table 1 summarizes the medical characteristics of the patients. More multiple pregnancies were found in the AC group (p=0.015). It was determined that the age of the mothers was significantly higher in the AC group (p=0.024).

Mothers' drug use was higher in the SC group (p=0.001). Free oxygen duration was found to be longer in the SC group (p=0,017)

Tables 2 and 3 summarize the echocardiographic characteristics. The groups were found to be similar in terms of anatomical, m-mode and tissue doppler systolic and diastolic functions by transthoracic ECHO (p=0.156).

Table 1. Demographic and medical characteristics of the groups

Characteristics	AC group babies* (n=25)	SC group babies** (n=25)	P value
GA (weeks), mean (SD)	31.3±1.8	30.7±2.5	.319
BW (grams), mean (SD)	1630.56±431.9	1385.6±472.6	.062
Sex, female, n (%)	11(44)	13(52)	.571
Age of Mother, mean (SD)	30.6±3.9	27.3±5.7	.024
Apgar at 1 min, n (%)	5.6±1.73	5.6±1.3	1
Apgar at 5 min, n (%)	6.7±1.13	6.5±1.12	.534
Maternal gestational diabetes n (%)	5(20)	1(4)	.082
Maternal preeclampsia, n (%)	3(12)	9(36)	.047
Chorioamnionitis, n (%)	1(4)	2(8)	.5
Preeclampsia, n (%)	3(12)	9(36)	.047
Antenatal steroid use, n (%)	11(44)	10(40)	.77
Maternal drug use, n (%)	0(0)	7(28)	.01
Type of birth, C/S, n (%)	25(100)	24(96)	.5
Respiratory Distress Syndrome, n (%)	8(32)	6(24)	.52
Surfactant use, n (%)	8(32)	7(28)	.758
Bronchopulmonary Dysplasia, n (%)	1(4)	3(12)	.39
Retinopathy of Prematurity, n (%)	3(12)	4(16.7)	.47
Patent Ductus Arteriosus, n (%)	1(4)	3(12)	.3
Discharge Time (day), mean (SD)	30,6±25,4	38,8±26,3	.27

*AC: Born from IVF pregnancy; **SC: Born from a spontaneous pregnancy

Table 2. Echocardiographic characteristics of the groups

Characteristics Characteristics	AC group babies* (n=25)	SC group babies** (n=25)	P value
Interventricular septal end diastole (mm), mean (SD)	3.6±.6	3.46±0.58	.19
Interventricular septal end systole (mm), mean (SD)	4.2±.64	4.17±.8	.82
Left ventricular internal diameter end diastole (mm), mean (SD)	11 (44)	13(52)	.571
Left ventricular internal diameter end systole (mm), mean (SD)	30.6±3.9	27.3±5.7	.024
Left ventricular posterior wall end diastole (mm), mean (SD)	5.6±1.73	5.6±1.3	1
Left ventricular posterior wall end systole (mm), mean (SD)	6.7±1.13	6.5±1.12	.534
Ejection fraction, %	73.1±2.47	73.6±3.6	.52
Fractional shortening, %	39.0±2.15	39.3±2.47	.72
Aortic annulus diameter (mm), mean (SD)	7.34±0.73	6.86 ±0.64	.14
Left atrium diameter (mm), mean (SD)	10±0.73	9.5±1.2	.3
Systolic pulmonary aortic pressure (mm), mean (SD)	16.6±4.5	22.4±6.9	.15
Right ventricular end-diastolic diameter (mm), mean (SD)	10.4±1.95	11.3±2	.36
Pulmonary annulus diameter (mm), mean (SD)	7.61±1.45	7.23±1	.59
Pulmonary artery flow (mm), mean (SD)	1±0.39	1±0.27	.48
Aortic artery flow (mm), mean (SD)	0.76±0.22	0.95±0.17	.13
Tricuspid Annular Plane Systolic Excursion, (mm), mean (SD)	7.32±1.32	6.63±1.16	.22
Mitral annular plane systolic excursion, (mm), mean (SD)	5.1±1	5.88±0.65	.06

*AC: Born from IVF pregnancy; **SC: Born from a spontaneous pregnancy

Discussion

It is estimated that more than 5 million children worldwide are born as a result of ART-induced pregnancy [12]. Although ART is generally considered safe, growing evidence suggests that ART

Table 3. Cardiac defets of the groups

Groups	ASD*	PFO**	VSD***	TY****	Normal	P value
AC group babies* (n=25)	9(%36)	6(%24)	3(%12)	1(%4)	6(%24)	.404
SC group babies* (n=25)	13(%52)	3(%12)	1(%4)	0(%0)	8(%32)	

ASD*: Atrial septal defect; PFO**: Patent foramen ovale; VSD***: Ventricular septal defect; TY****: Tricuspid regurgitation

is associated with worse perinatal outcomes and an increased risk for congenital malformations [13]. Rapid technological progress and the rapid increase in the popularity of ART techniques bring the importance of safety to the front [12]. In this context, there are many studies evaluating the health status of AC-infants as well as prenatal, perinatal and long-term risks. Nonetheless, as the rate of invasive intervention in the formation of conception increases, worse results may be encountered. Wen et al. have shown that IVF/ICSI may be more harmful than natural pregnancies, and ICSI may be more harmful than traditional IVF [14]. However, in the studies by Olson et al., there was no difference in the rates of defective births among all IVF offspring after ICSI or after transfer of cryopreserved embryos [15].

Infertility treatments increase the risk of cardiovascular disease due to the high level of hormones they are exposed to, damage to the endothelial tissue, and predisposition to coagulopathy [16]. As a consequence, it has been observed that sub-fertile individuals are more associated with metabolic diseases and cardiovascular disease later in their lives [17]. In our study, the groups were similar in terms of maternal disorders. However, maternal age was higher than expected in the AS group. We found that mothers tended to use more medication during SC pregnancies. We attributed this result to lower levels of anxiety about infant loss compared to the other group.

As a result of possible problems in the fetal development of AC-infants, cardiovascular remodeling has become one of the dreaded manifestations, and indeed some studies have reported the emergence of cardiovascular remodeling [18]. In this study, we did not find any difference between IVF and spontaneous pregnancy babies in terms of systolic and diastolic functions in CHD, m-mod and tissue dopplers. Previous studies have reported a slightly higher risk of CHD in ART-conceived infants compared to SC infants [19,20]. In a meta-analysis, Hooarsan et al. showed that ART-conceived infants were at a 43% higher risk of CHD (OR: 1.43, 95% CI: 1.30-1.60) compared to SC infants [21]. A cohort study reported the incidence of mild CHD in fetuses born with ART as 2.75% (10 out of 363 fetuses) [22]. Overall, previous meta-analyses have concluded that children born with IVF/ICSI pregnancy are at an increased risk for cardiovascular and other system defects [15].

ART techniques have also been associated with cardiovascular abnormalities. This has been attributed to multifactorial causes at the molecular level. Epigenetic changes, increased prematurity, and the ratio of low birth weight associated with ART are thought to cause poor cardiovascular and overall outcomes [22].

The limitations of this study include the small number of cases in the study and control groups. The ART group, which included only IVF infants, could not enclose infants from different ART procedures, and hence the results could not be compared among themselves.

Conclusion

In conclusion, although not confirmed by the results of our study, taking into account the literature, it is possible to say that IVF infants are at higher risk for CHD than SC infants. These infants require closer pediatric cardiology follow-up starting from fetal life to assess cardiac anatomy and function. Early diagnosis of possible cardiac diseases is vital for pre- and post-natal management and ultimately for the survival of the infant. Studies should be focused on understanding and eliminating the pathophysiologies increasing the risk of CHD during ever-increasing ART practices.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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